

# Clinical Profile of Hypoglycaemia in Neonates at Risk in a Tertiary Care Teaching Institute in Southern India: A Longitudinal Study

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## ABSTRACT

**Introduction:** Hypoglycaemia is common in babies at risk. Without early detection, timely diagnosis and treatment, hypoglycaemia can cause disastrous consequences on neurological and developmental outcomes. Therefore, continuous monitoring of blood glucose levels in babies at risk should be done to reduce its impact.

**Aim:** To describe the clinical profile and sequential blood sugar levels in the first four postnatal days in at-risk neonates and to identify the risk group of neonates with recurrent hypoglycaemia.

**Materials and Methods:** This was a longitudinal study done in the Neonatal Intensive Care Unit (NICU) and Special Newborn Care Unit (SNCU) of a tertiary care teaching institute; Sri Avittam Thirunal Hospital (SATH), Government Medical College, Thiruvananthapuram, Kerala, India, from October 2017 to October 2018. Neonates admitted with risk factors for hypoglycaemia according to 'National Neonatology Forum' clinical guidelines with low capillary blood sugar (<40 mg/dL) within the first two to four hours of life were included in the study. These neonates were followed-up clinically till fourth postnatal day with glucose monitoring. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 22. Categorical variables were expressed as proportions and compared using the Chi-square test. A p-value <0.05 was considered statistically significant.

**Results:** A total of 368 'at risk' neonates had hypoglycaemia at admission (2 to 4 hours) and of these 200 (54.3%) developed recurrent hypoglycaemia. Out of the neonates with recurrent hypoglycaemia, 150 (75%) were preterm and 50 (25%) were term. The preterm Small for Gestational Age (SGA) had a higher chance of developing recurrent hypoglycaemia than preterm Appropriate for Gestational Age (AGA) and Large for Gestational Age (LGA) (p-value=0.0256). Although, 102 (40.2%) preterm had asymptomatic hypoglycaemia, 90 (78.9%) term neonates showed symptoms of hypoglycaemia. The major clinical manifestation was jitteriness in those with a single episode 31 (18.45%) and lethargy/poor activity in those with more than one episode 66 (33%). The blood glucose levels less than 25 mg/dL at admission was significantly associated with the occurrence of a repeat episode of hypoglycaemia (p-value=0.028).

**Conclusion:** Blood glucose monitoring in neonates with risk factors is mandatory as 54.3% of neonates developed recurrent hypoglycaemia. Of these, preterm SGA had a high chance of developing recurrent hypoglycaemia. The variable presentations in neonatal hypoglycaemia indicates the need for detailed and thorough clinical examination with glucose monitoring in these at-risk neonates. Initial blood glucose level less than 25 mg/dL was significantly associated with recurrent hypoglycaemia.

**Keywords:** Blood sugar, Brain injury, Glucose monitoring, Lethargy, Low birth weight, Newborn babies, Preterm

## INTRODUCTION

Neonatal hypoglycaemia is one of the most common biochemical abnormalities encountered in the newborns. The overall incidence of neonatal hypoglycaemia is 1 to 5 per 1,000 live births and in high-risk neonates, incidence is upto 30% [1,2]. The glucose requirement of the brain is about 90% of the total glucose requirement in neonates. The maintenance of normal blood glucose levels in newborns depends on adequate glycogen stores, maturation of pathways of glycogenolysis, gluconeogenesis and adequate endocrine response. This hormonal metabolic adaptation after birth fails to a variable extent in preterm and SGA infants [3]. Therefore, hypoglycaemia is more common in the first 72 hours of life [4]. Hypoglycaemia may be asymptomatic or symptomatic in the form of lethargy, refusal to feed, apathy, irritability, jitteriness, apnoea, hypothermia, cyanosis and seizures which are non specific and can be missed easily especially in the sick neonate. Reversibility of symptoms on giving glucose confirms the diagnosis as symptomatic hypoglycaemia.

Both symptomatic and asymptomatic hypoglycaemia is associated with poor neurodevelopmental outcome [5-8]. Therefore, we have to emphasise upon prevention, early detection and treatment of asymptomatic hypoglycaemia [9,10]. The definition of neonatal hypoglycaemia is still controversial because of the lack of significant correlation among plasma glucose concentration, clinical signs and long-term sequelae. In a multicenter study by Lucas A et al., in 1988, a blood glucose concentration <47 mg/dL was the critical threshold associated with adverse neurodevelopmental outcome even in the healthy, term, AGA infants and this value was taken for long time as the threshold for hypoglycaemia intervention [11]. Currently, the operational threshold for hypoglycaemia is blood glucose value of <40 mg/dL or plasma glucose <45 mg/dL [12,13]. Although, the groups of babies at the highest risk of hypoglycaemia are well-defined, the optimal frequency and duration of screening for hypoglycaemia and the threshold at which treatment would prevent brain injury remains uncertain [14]. Since hypoglycaemia

is common in high-risk neonates, screening of blood glucose levels along with clinical monitoring is important in the diagnosis and proper management of these neonates to reduce morbidity and mortality. The most common sequelae of hypoglycaemia are disturbances of neurological development and intellectual function, although minor deficits, especially spasticity, ataxia and seizure disorders can also occur. A recent Indian study had concluded that neonatal hypoglycaemia was the most common aetiology of remote symptomatic infantile onset epilepsy [15].

There is a scarcity of literature on recurrent hypoglycaemia in “at-risk” neonates and it is the recurrent hypoglycaemia which is responsible for the long-term adverse neurological problems [16-18].

The present study was conducted on “at-risk” newborn babies and admitted in the inborn nursery at the institution, and the authors' goals were to identify the pattern of hypoglycaemia in these babies, describe their clinical profile and to find out the risk factors for single episode versus recurrent episodes of hypoglycaemia.

## MATERIALS AND METHODS

This was a longitudinal study done in the NICU and SNCU of Sri Avittam Thirunal hospital, Government Medical College, which is a tertiary care teaching hospital in Southern Kerala, Thiruvananthapuram, India. The study was carried out for a period of one year from October 2017 to October 2018 after taking ethical clearance from the Institutional Ethics Committee. The IEC clearance certificate number was 08/07/2017/MCT.

**Inclusion criteria:** All newborn babies admitted in the NICU and SNCU who were “at-risk” for hypoglycaemia and were hypoglycaemic (capillary blood sugar <40 mg/dL) within the first two to four hours of birth were included in the study. The newborns included as “at-risk” newborns were adapted from the “National Neonatology Forum (NNF) clinical practice guidelines” [19]; These were low birth weight infants (<2500 grams), preterm infants (≤37 completed weeks), SGA, Infant of Diabetic Mothers (IDM), infants with Rh-haemolytic disease, infants born to mothers receiving therapy with terbutaline/propranolol/labetalol/oral hypoglycaemic agents, infants with morphological intrauterine retardation (IUGR), any sick neonate such as those with perinatal asphyxia, polycythaemia, sepsis and shock in the acute phase of illness.

**Exclusion criteria:** Newborns with gestational age less than 26 completed weeks, those with multiple congenital anomalies with or without complex congenital cyanotic heart disease, neonates without follow-up for the first four days after birth and “at-risk” newborns whose parents were not willing to give consent for the study were excluded from the study.

**Sample size calculation:** Sample size was calculated as:

$$N = 4pq/d^2$$

Where p is the prevalence of hypoglycaemia in high-risk neonates i.e., 33.33% [18]

$$q = 1 - p \text{ which is } 66.67\%$$

Taking ‘d’ (precision) to be 5; the calculation is as follows:

$4 \times 33.33 \times 66.67 / 25$  ie; The minimum sample required for the study was 355.5 which was taken as 356 for final analysis.

## Study Procedure

After obtaining informed consent from the parents, all consecutive eligible neonates were recruited into the study. Antenatal medical records of mothers of all included neonates were examined for

maternal risk factors such as gestational hypertension, gestational and overt diabetic, seizure disorder, heart disease, Systemic Lupus Erythematosus (SLE) and other connective tissue disorders, parity, mode of delivery, gestation, birth weight and details entered into the proforma. Parents were explained about baby's risk for hypoglycaemia and consent for blood glucose estimation at regular intervals was obtained. Under aseptic precautions heel prick was made and capillary blood glucose was checked using glucometer. The right or left heel of neonates was disinfected using a cotton and 70% methylated spirit. The disinfected site was allowed to air dry for 30 seconds and a sterile lancet was used to prick the heel.

Neonates admitted into the neonatal unit had their Random Blood Sugar (RBS) done at admission within 2 to 4 hours using rapid glucose test strip mounted on Accu-chek (Active) glucometer device manufactured by (Roche Diagnostics GmbH D- 68298 Mannheim, Germany) which could be read and displayed in 10 secs. Blood glucose value of <40 mg/dL was taken as hypoglycaemia in the first day after birth and <45 mg/dL after 24 hours. Confirmation of blood glucose was done by plasma glucose measured by glucose oxidase method in the laboratory, only if the capillary glucose level was less than 25 mg/dL or if the baby had symptoms of poor activity, poor feeding, lethargy, drowsiness, apnoea, jitteriness, cyanosis or seizures.

Those newborns with severe and symptomatic hypoglycaemia were monitored with blood sugar more frequently (hourly or 2 hourly) than those whose blood sugar remained stable with oral/ intravenous (i.v.) fluids (6 hourly or twice daily). These neonates were followed-up for four days with relevant clinical examination and blood glucose monitoring and these were noted in a semi-structured proforma. Although deliberate intervention was not performed, the newborns were managed and treated as per standard protocol of NNF guidelines [19].

## Definition and classification of hypoglycaemia [20-22].

**Hypoglycaemia** was defined as a blood glucose value of less than 40 mg/dL (Plasma glucose less than 45 mg/dL) within 24 hours and <45 mg/dL (plasma glucose <50 mg/dL) after 24 hours.

**Severe hypoglycaemia** was defined as blood glucose <25 mg/dL within 24 hours and <35 mg/dL after 24 hours (always confirmed with plasma glucose values).

**Prolonged hypoglycaemia-** If neonates were still hypoglycaemic one hour after intervention.

**Recurrent hypoglycaemia-** Neonates having more than one hypoglycaemic episode.

## STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software version 22. Categorical variables were expressed as proportions and were compared using the Chi-square test. A p-value of <0.05 was considered statistically significant.

## RESULTS

The demographic variables of neonates with hypoglycaemia are shown in [Table/Fig-1]. Maternal risk factors were present in 301 (84.2%). Of this, gestational hypertension accounted for 132 (42.6%). Of the total neonates, 254 (69%) were preterm, low birth weight (LBW) were 290 (78.8%) and small for gestational age (SGA) neonates were 228 (61.96%). Infant of diabetic mother (IDM) accounted for 97 (26.35%) of the neonates, but there were only 12 (3.26%) LGA babies.

Out of the total of 368 neonates who had hypoglycaemia, 45.65% (n=168) neonates suffered single episode of hypoglycaemia which included 104 (61.9%) preterm and 64 (38.1%) term whereas in

Variables	Number (%)
<b>Gender</b>	
Male	210 (57.06%)
Female	158 (42.94%)
<b>Gestation</b>	
Preterm	254 (69.02%)
Term	114 (30.98%)
<b>Mode of delivery</b>	
Normal	146 (39.67%)
LSCS	222 (60.33%)
<b>Singleton vs multiple births</b>	
Singleton	312 (92.58%)
Twin	19 (5.64%)
Triplets	6 (1.78%)
<b>Parity</b>	
Primipara	220 (59.78%)
Multipara	148 (40.21%)
<b>Birth weight</b>	
LBW (<2.5 KG)	290 (78.80%)
<b>Birth weight classification~</b>	
LGA	12 (3.26%)
AGA	128 (34.78%)
SGA	228 (61.96%)
<b>Maternal risk factors</b>	
Gestational hypertension	132 (42.6%)
Gestational diabetics	45 (14.5%)
Gestational hypertension and diabetics	36 (11.6%)
Overt diabetics	16 (5.16%)
Seizure disorder	21 (6.77%)
Seizure disorder and Gestational hypertension	26 (8.38%)
Heart disease	14 (4.5%)
Heart disease and Gestational hypertension	12(3.9%)
SLE and other connective tissue diseases	8 (2.58%)
No Maternal risk factors	58 (15.76%)
<b>Classification of Preterm babies*</b>	
Late preterm >34 to 37 weeks)	76 (20.65%)
>32 to ≤34 weeks	68 (18.47%)
>28 to ≤34 weeks	71 (19.29%)
>26 to ≤28 weeks	39 (10.6%)
<b>Neonatal co-morbidities</b>	
IDM	97 (26.35%)
Sick neonates (Perinatal asphyxia, sepsis, shock)	67 (18.2%)

**[Table/Fig-1]:** Demographic variables of neonates with hypoglycaemia (N=368).

LSCS: Lower segment caesarean section; LBW: Low birth weight; \*percentages are calculated from total sample size (N=368); LGA: Large for Gestational Age, AGA: Appropriate for Gestational Age, SGA: Small for Gestational Age

neonates who had more than one episode of hypoglycaemia (persistent and recurrent hypoglycaemia, n=200), there were 150 (75%) preterm and 50 (25%) term. Recurrent hypoglycaemia was more common in preterm than in term and this was statistically significant (p-value=0.0091) as shown in [Table/Fig-2].

On comparing the birth weight of neonates who suffered from single episode of hypoglycaemia (n=168); low birth weight (LBW) was 112 (66.66%), normal birth weight (NBW) was 54 (32.14%) and macrosomic were 2 (1.2%). The occurrence of recurrent hypoglycaemia (n=200) was

Variables	Single episode at admission (n=168) n (%)	Recurrent/Prolonged (n=200) n (%)	$\chi^2$ /p-value
<b>Gestational age</b>			
Preterm	104 (61.9%)	150 (75%)	$\chi^2$ value 6.72 p-value=0.0091*
Term	64 (38.1%)	50 (25%)	
<b>Birth weight</b>			
LBW	112 (66.67%)	178 (89%)	$\chi^2$ value 35.13 p-value <0.001**
NBW	54 (32.14%)	16 (8%)	
Macrosomia	2 (1.2%)	6 (3%)	
<b>Birth weight classification</b>			
SGA	96 (57.14%)	132 (66%)	$\chi^2$ value 4.77 p-value=0.092
AGA	68 (40.5%)	60 (30%)	
LGA	4 (2.4%)	8 (4%)	

**[Table/Fig-2]:** Risk factors of single episode of hypoglycaemia and recurrent hypoglycaemia.

\*p value <0.05 statistically significant; \*\*p value <0.001 statistically highly significant; LBW: Low birthweight; NBW: Normal birthweight

more among LBW babies (89%, n=178) when compared with normal birth weight babies (8%, n =16) with (p value<0.001) [Table/Fig-2].

About 57.14% (n=96) babies with single episode of hypoglycaemia were SGA, 40.5% (n=68) were AGA and 2.4% (n=4) were LGA. About 66% (n=132) babies with recurrent episode of hypoglycaemia were SGA, 30% (n=60) were AGA and 4% (n=8) were LGA (p=0.092) [Table/Fig-2].

Preterm and term neonates with hypoglycaemia classified based on birthweight for gestational age are shown in [Table/Fig-3]. There were 104 preterm neonates in the single episode hypoglycaemia group (n=168) in which preterm SGA was 58 (55.77%) and preterm AGA was 46 (44.23%). There were 150 preterm neonates in the recurrent hypoglycaemia group (n=200) in which preterm SGA was 104 (69.33%), preterm AGA was 44 (29.33%) and preterm LGA was 2 (1.33%) which was statistically significant for preterm SGA (p-value=0.025). Also, as seen in [Table/Fig-3], recurrent hypoglycaemia was not significantly higher in term SGA Vs term AGA (p-value=0.56).

Variables	Single episode n (%)	Recurrent/Prolonged episode n (%)	p-value
<b>Preterm babies</b>	104 (100%)	150 (100%)	0.0256*
Preterm SGA	58 (55.77%)	104 (69.33%)	
Preterm AGA	46 (44.23%)	44 (29.33%)	
Preterm LGA	0	2 (1.33%)	
<b>Term babies</b>	64 (100%)	50 (100%)	0.56
Term SGA	38 (59.37%)	28 (56%)	
Term AGA	22 (34.37%)	16 (32%)	
Term LGA	4 (6.25%)	6 (12%)	

**[Table/Fig-3]:** Preterm and term neonates with hypoglycaemia classified based on birthweight for gestational age.

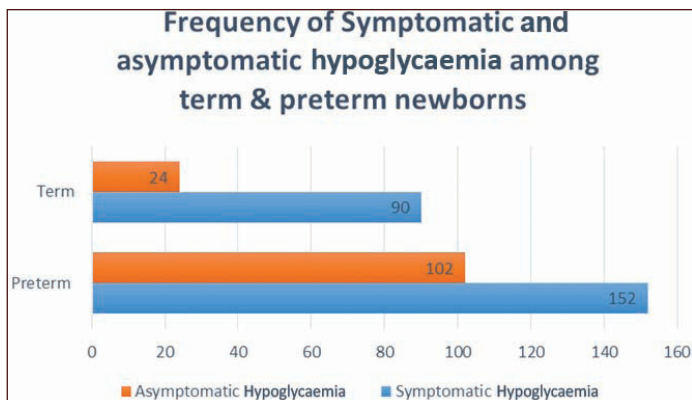
\*p-value <0.05 statistically significant

[Table/Fig-4] compares the blood sugar level at the time of admission between neonates with single episode at admission and more than one episode. This depicts that blood glucose levels less than 25 mg/dL at admission was significantly associated with occurrence of repeat episode of hypoglycaemia (p-value=0.028).

[Table/Fig-5] shows that 102 (40.2%) preterm had asymptomatic hypoglycaemia and 152 (59.8%) had symptomatic hypoglycaemia. Also, 90 (78.9%) term neonates showed symptoms of hypoglycaemia whereas 24 (21.1%) had asymptomatic hypoglycaemia.

Blood glucose level (mg/dL)	Single episode (n=168)	More than one episode (n=200)	p-value
31 to 39	65 (38.69%)	73 (36.5%)	0.028*
25 to 30	65 (38.69%)	58 (29%)	
<25	38 (22.62%)	69 (34.5%)	

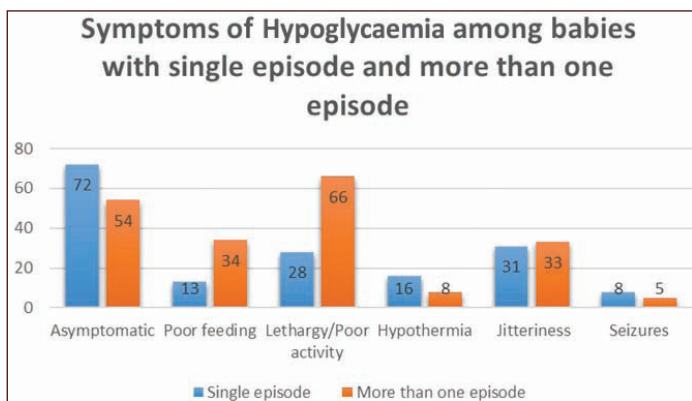
**[Table/Fig-4]:** Blood sugar level at the time of admission between neonates with single episode at admission and more than one episode. \*p value <0.05 - statistically significant



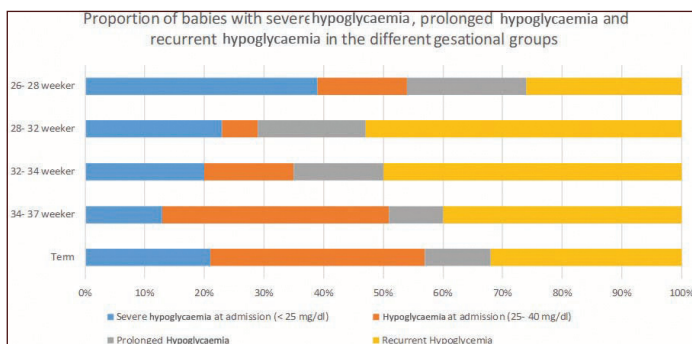
**[Table/Fig-5]:** Symptomatic Vs asymptomatic hypoglycaemia in term and preterm neonates.

[Table/Fig-6] shows symptoms of hypoglycaemia with single episode and recurrent episodes. Asymptomatic hypoglycaemia was more common in neonates with single episode (n=72/168; 42.85%) than in those with recurrent episodes (54/200; 27%). Lethargy/poor activity accounted for 33% (n=66/200) of the symptoms in neonates with recurrent episode of hypoglycaemia.

It was seen that 45.65% (168/368) experienced single episode of hypoglycaemia, 13.86% (51/368) experienced two episodes of hypoglycaemia and 40.49% (149/368) neonates experienced more than two episodes of hypoglycaemia in the first four days of life.



**[Table/Fig-6]:** Symptoms of hypoglycaemia with single episode and more than one episode. Single episode n=168, Two or more than two episode n=200



**[Table/Fig-7]:** Proportion of neonates with severe hypoglycaemia, prolonged hypoglycaemia and recurrent hypoglycaemia in different gestational groups.

Out of 54.35% (200/368) neonates with recurrent episode, 38% (76/200) developed hypoglycaemia within 1 day (from 4 to 24 hours), 36% (72/200) on day 2, 16.5% (33/200) on day 3 and 9.5% (19/200) on day 4.

[Table/Fig-7] shows the proportion of neonates with hypoglycemia at admission (25 mg/dL-40 mg/dL), severe hypoglycaemia (< 25mg/dl), prolonged hypoglycemia and recurrent hypoglycemia in different gestational groups as term babies, late preterm (>34 to 37 weeks), >32 to ≤34 weeks, >28 to ≤34 weeks and >26 to ≤28 weeks.

## DISCUSSION

In our study, maternal risk factors were present in 84.24% (n=310) and out of this gestational hypertension accounted for 42.6% (n=132). Mothers with gestational and overt diabetics accounted for 14.5% (n=45) and 5.16% (n=16) respectively, but LGA contributed to only 3.26% (n=12). Those with both gestational hypertension and diabetics were 11.6% (n=36). Gestational hypertension was the most common risk factor present in many studies [23-28]. In 2004, a study done in Kerala by Sasidharan CK et al., shows that gestational hypertension was the most significant maternal risk factor associated with neonatal hypoglycaemia, accounting for 16.5%, which is lower than our study possibly because of the cohort of high-risk mothers in our tertiary level teaching hospital. Also, the ratio of preterm and term neonates with hypoglycaemia in our study (2.23: 1) was similar to this Kerala study [28].

In our study, recurrent hypoglycaemia was more common in preterm babies than in term babies and this was statistically significant (p-value=0.0091). Also, neonates with LBW had recurrent hypoglycaemia which was statistically significant (p-value <0.0001). This was similar to other studies in which higher chances of hypoglycaemic episodes were present in low-birth weight babies [29,30]. The occurrence of recurrent hypoglycaemia was significantly higher for preterm SGA babies (p-value=0.025) in our study. But when authors considered all SGA babies together, this was no statistically significant (p-value=0.092). This was probably due to the fact that the majority (70.3%, n=90) of AGA babies were preterm and they had an increased risk of recurrent hypoglycaemia. Also in our study, recurrent hypoglycaemia was not significantly higher in term SGA verses term AGA (p-value= 0.56), probably because all term AGA admitted were sick neonates with perinatal asphyxia, early onset neonatal sepsis and shock (33.33%, n=38) and they had episodes of recurrent hypoglycaemia. In a study by Amarendra M et al., premature neonates were 27%, SGA were 30%, LGA were 6% and IDM were 21% [24]. In a study by Singh YP et al., hypoglycaemia was more common in preterm as compared to term babies (19.05% vs 14.42%) and was present in 23.08% SGA babies [25]. In a study conducted by Zhou W et al., it was found that premature neonates, LBW babies and neonates with perinatal asphyxia had greater susceptibility to hypoglycaemia [16].

In our study, out of the total neonates, 34.23% (n=126) were asymptomatic and 65.7% (n=242) were symptomatic. Of these, 40.2% (n=102/254) preterm were asymptomatic and 78.9% (n=90/114) term neonates were symptomatic. Among the symptoms, lethargy /poor activity accounted for 38.8% of symptoms and jitteriness accounted for 26.4%. In a study by Amarendra M et al., out of 100 children with hypoglycaemia; 63 (63%) were asymptomatic and 37 (37%) presented with symptoms and most common symptoms of hypoglycaemia were poor feeding (69%), lethargy (17.8%), jitteriness (11.9%), seizure (9.5%), hypotonia (2.3%) and 1.2% presented with cyanosis and respiratory abnormality [24]. In another study by Babu MR et al., 55% babies had asymptomatic hypoglycaemia [27]. In the study by Sasidharan CK et al., 59.3% babies were asymptomatic and

out of the those with symptoms, the common symptoms were poor feeding (70.27%), lethargy (18.92%), jitteriness (10.81%), irritability (5.40%), hypotonia (2.70%) and cyanosis (2.70%) [28]. In a study by Dhananjaya CD and Kiran B, majority of hypoglycaemic babies were preterm; asymptomatic hypoglycaemia (65.21%) was predominantly noticed in preterm babies whereas term babies had symptomatic hypoglycaemia (58.82%) with jitteriness for 55.55% and lethargy for 30% babies [31]. In a study by Anjum R et al., symptoms of neonatal hypoglycaemia were temperature instability (39%), jitteriness (34%), lethargy (32%), cyanosis (12%), tachypnoea (8%), apnoea (6%) and seizures (9%) [32].

In our study, 45.65% (168/368) neonates developed only one episode of hypoglycaemia on admission within four hours. Out of 54.35% (200/368) neonates with recurrent episode, 38% (76/200) developed hypoglycaemia within one day (from 4 to 24 hours), 36% (72/200) on day 2, 16.5% (33/200) on day 3 and 9.5% (19/200) on day 4. In a study by Thinesh kumar J et al., hypoglycaemia was detected in first 24 hours in 29% of the new-borns, 26.8% had hypoglycaemia in day 2 of life and in day 3 of life 21.4% were found to be hypoglycaemic. Also, 22.7% were found to be hypoglycaemic beyond 72 hours of life [18]. In a study by Zhou W et al., hypoglycaemia always occurred within one week after birth, especially within three days after birth [16]. In a study by Harris DL et al., one-half of the babies (260/514, 51%) became hypoglycaemic (<2.6 mM), 97 (19%) had severe hypoglycaemia ( $\leq 2.0$  mM), and 98 (19%) had more than one episode. Most episodes (315/390, 81%) occurred in the first 24 hours [17]. In another study by OzgeY and Deniz AI, recurrent hypoglycaemia, which is important for long-term adverse neurological effects, was observed in 24.1% of all babies with hypoglycaemia and recurrent hypoglycaemia was seen more frequently in the SGA babies. Of the recurrent episodes, 34 (34.6%) were found to occur within eight hours of the initial episode and 82 (83.6%) within 24 hours [33].

There are many studies that highlight the importance of determining the developmental outcome of babies who have experienced recurrent hypoglycemia. A few of such studies are discussed below:

One of the earliest studies was by Lucas A et al., in which hypoglycaemia above five or more days decreased the Bayley motor and mental scales by 13 and 14 points respectively, in corrected 18<sup>th</sup> months. The incidence of neurological defects such as cerebral palsy and developmental retardation (mental-motor scale  $\leq 70$  vs) increased 3.5 times (95% confidence interval 1.3 to 9.4) [11]. In a study by Duvanel CB et al., in 1999, neonates with recurrent hypoglycaemia had persistent neurodevelopmental and physical growth deficits until five years of age. Also, recurrent hypoglycaemia was more predictive for long-term neurodevelopmental defects than the severity of a single episode [34]. In a Workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development, hypoglycaemia that is symptomatic, recurrent, or persistent has been shown to be associated with neuromotor damage [35].

In a study by Hosagasi NH et al., [20], recurrent hypoglycaemia was seen in 30% of all hypoglycaemic newborns. There was no relationship between groups of late preterm, LGA, SGA/IUGR, and IDM newborns concerning severe, prolonged and recurrent hypoglycaemia. Occipital and parietal lobes were most severely affected regions of the brain on imaging techniques in infants who suffered from brain damage as a result of neonatal hypoglycaemia. On neurodevelopment follow-up, the mental and psychomotor developmental indexes of the children who suffered from hypoglycaemia during newborn period were significantly low.

In the CHYLD study by McKinlay CJD et al., at 4.5 years of follow-up, impaired executive and visual motor functions (three-fold risk)

were observed with especially increased risk for those with severe (<2.0 mmol/L), recurrent, or clinically undetected episodes [36].

According to another study by McKinlay CJD et al., neonatal hypoglycaemia was not associated with an adverse neurologic outcome when treatment was provided to maintain a blood glucose concentration of at least 47 mg/dL. Also, in this study, although neonatal hypoglycaemia was commonly observed in 216/404 neonates (53%), due to regular measurement of blood glucose concentrations and early treatment, recurrent hypoglycaemia was infrequent. The recurrent hypoglycaemia pattern in this study was  $\geq 1$  episode 216 (53%);  $\geq 3$  episodes 34 (8%); Episodes on  $\geq 3$  days in first week 12 (33%) [37].

From a study in 2020 by Rasmussen AH et al., neonatal hypoglycaemia <1.7 mmol/L treated to >2.5 mmol/L, without other severe risk factors for neurodevelopmental outcome showed a lower fine motor function, especially in boys, within the normal range at follow-up visits. No changes in cognitive function or behaviour were found [38].

In a study by Sharma A et al., if neonatal hypoglycaemia was not treated in a timely manner, the poor outcomes were directly proportional to the extend, severity and duration of hypoglycaemia. They stated in their study that all neonates with hypoglycaemia have to be classified into transient and recurrent/persistent hypoglycaemia. These latter neonates have to be referred to a tertiary level with advanced diagnostic and therapeutic interventions [39].

The glycaemic threshold and time threshold values of Neonatal Hypoglycaemic Brain Injury (NHBI) still remains undefined. Neonatal permanent brain injury leading to cognitive impairment, vision disturbance, occipital lobe epilepsy, hearing impairment, cerebral palsy and secondary epilepsy can result from persistent or recurrent neonatal hypoglycaemia [14,40,41].

Neonatal hypoglycaemia is a common metabolic disorder in newborns and is a preventable cause of brain damage. The goal of management is to prevent or minimise brain injury but the optimal frequency and duration of screening for hypoglycaemia, as well as the threshold at which treatment would prevent brain injury still remains uncertain. Our study explored the concept of recurrent hypoglycaemia in at-risk neonates which is associated with poor neurodevelopmental outcome according to literature. This is also a genuine attempt to generate a baseline data which would be of value in further studies on recurrent hypoglycemia in at-risk neonates.

### Limitation(s)

The study group included only neonates admitted in NICU and SNCU and not all neonates delivered in the hospital; so, the data may not represent the entire population. Outborn babies were also not included. Neonates with persistent hypoglycemia beyond seven days were not followed-up in the present study. Authors followed-up with neonates only for the first four days. Also, the neurodevelopmental outcome of neonates was not assessed in the present study.

### CONCLUSION(S)

Recurrent hypoglycaemia was seen in more than 50% of 'at-risk' neonates and is more common in preterm than in term babies. The low birth weight and preterm SGA had higher chances of developing recurrent hypoglycaemia. Symptomatic hypoglycaemia was seen in 78.9% term neonates with lethargy/poor activity accounting for majority of the symptoms (33%), but in preterm, 40.2% had asymptomatic hypoglycaemia. The blood glucose levels less than 25 mg/dL at admission was significantly associated with occurrence of repeat episodes of hypoglycaemia. Identification of risk factors for hypoglycaemia and in particular recurrent hypoglycaemia, along

with proper monitoring of blood glucose levels is important to plan early treatment and prevent neurological damage.

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### AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

### PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Feb 07, 2022
- Manual Googling: Apr 18, 2022
- iThenticate Software: May 10, 2022 (23%)

### ETYMOLOGY: Author Origin

Date of Submission: **Feb 03, 2022**  
Date of Peer Review: **Feb 24, 2022**  
Date of Acceptance: **Apr 20, 2022**  
Date of Publishing: **Jun 30, 2022**